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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/797,613	03/09/2004	Brian Zambrowicz	07705.0001-01000	3971

22852 7590 07/19/2006

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/797,613	ZAMBROWICZ ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-46* is/are pending in the application.

4a) Of the above claim(s) *21-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7-16-04, 2-1-05*. 8-9-2005 5-24-06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group II, claims 34-46, in the reply filed on 5-24-06 is acknowledged. The traversal is on the ground(s) that groups I and II are drawn to similar intended result of disruption of a gene in the genome of a murine embryonic stem cell and vectors in groups I and II can be used for similar purpose, and further both groups have same classification. This is not found persuasive because a vector comprising a 5' gene trap cassette and a 3' gene trap cassette is different from a vector comprising only a 3' gene trap cassette, and the transgenic mouse produced would differ phenotypically and physiologically. Although they may have same classification, however, a 5' + 3' gene trap vector and a 3' gene trap vector differ in their mechanism of disrupting gene in a genome and the identification of the ES cells containing the vector. They are materially different methods that differ in method steps, reagents used, dosages and schedules used, response variables, and criteria of success. They require separate searches and the search would not be coextensive. There would be serious burden on examiner to search both groups I and II.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 21-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5-24-06.

Applicants' preliminary amendment filed 7-16-04 has been entered. Claims 1-20 have been canceled. Claims 21-46 have been added. Claims 21-46 are pending. Claims 34-46 are under consideration.

Specification

This application contains sequence disclosures that are encompassed by the definition for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there is no sequence identifier for the nucleotide sequence in Figures 3-5 or in the "BRIEF DESCRIPTION OF THE DRAWINGS". Each nucleotide sequence is required to have a sequence identifier. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 34-46 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: How to make a transgenic mouse comprising the vector from the selected ES cell comprising the vector, how to make a somatic transgenic mouse, how to make a germ line transgenic mouse, and how to administer the selected ES cell comprising the vector to make either a somatic transgenic mouse or a germ line transgenic mosue.

5. Claim 40 recites the limitation "said splice acceptor" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. There is no "splice acceptor" in claim 34.

6. Claim 41 recites the limitation "said polyadenylation sequence" in line 2. There is insufficient antecedent basis for this limitation in the claim. There is no "polyadenylation sequence" in claim 34.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 34-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 34-46 are drawn to a method of making a transgenic mouse comprising a vector comprising a promoter, an exon sequence located 3' from said promoter and a splice donor sequence located at the 3' end of said exon sequence, by introducing said vector into murine embryonic stem cells, selecting a murine cell that comprises the vector and making a transgenic mouse from the selected murine ES cell. Claims 36, 37, 45 and 46 specify further identifying at least one trapped cellular exon. Claims 38 and 39 specify the transgenic mouse is a somatic transgenic mouse and a germ line transgenic mouse, respectively. Claims 42 and 43 specify the exon sequence encodes an enzymatic marker, a recombinase or a fluorescent marker. Claim 44 specifies the vector is a viral vector or a retroviral vector.

The specification only discloses the preparation of PGKbtkSD cassette and introduction of said cassette into embryonic stem cells (p. 61. 62). The specification states that "[t]ransgenic animals and cells produced using the presently described library and/or vectors are useful for the study of basic biological processes and the development of therapeutics and diagnostics for diseases" (p. 32). The claims encompass making a somatic transgenic mouse or a germ line

transgenic mouse comprising a vector comprising a 3' gene trap cassette by introducing said vector into murine embryonic stem (ES) cells and selecting a murine ES cell comprising said vector. The specification fails to provide adequate guidance and evidence for how to make a somatic transgenic mouse or a germ line transgenic mouse comprising the claimed 3' gene trap cassette by using murine ES cells. The specification also fails to provide adequate guidance and evidence for how to use the produced somatic transgenic mouse or a germ line transgenic mouse for the study of basic biological processes and the development of therapeutics and diagnostics for diseases.

3' gene trap vector is designed to integrate into introns or genes such that the gene integrated is over-expressed, silenced, or under-expressed, and a fusion protein encoded by the exon sequence in the vector and the exon sequence of the integrated gene is expressed. The integration of a 3' gene trap vector into genome is non-homologous recombination. Therefore, whether the integrated gene is over-expressed, suppressed, or under-expressed depends on the integration site of the 3' gene trap vector and its surrounding genomic sequence context. Whether a somatic transgenic mouse or a germ line transgenic mouse can be made or have a phenotype depends on how the integrated gene is expressed and what kind of gene product is expressed. Maybe not gene product is expressed because there is silencer sequence at the integration site of the 3' gene trap vector. Absent a gene product, no transgenic mouse having a phenotype other than the wild-type phenotype can be produced. If there is a gene product expressed after integration, different gene products could result in different phenotypes in the transgenic mouse produced. Thus, it was unpredictable at the time of the invention whether a somatic transgenic mouse or a germ line transgenic mouse could be made by using the claimed

method and whether there is any phenotype of the transgenic mouse produced by the claimed method. The transgenic mouse produced by the claimed method must have a use. Absent a phenotype of the transgenic mouse, one skilled in the art would not know how to use the transgenic mouse produced by the claimed method, for example, use of the produced transgenic mouse for the study of basic biological processes and the development of therapeutics and diagnostics for diseases as disclosed in the specification.

Further, the genetic background of the transgenic mice has a large impact on the resulting phenotype of the transgenic mice. Mogil et al., 1999 (Pain, Vol. 80, pages 67-82) reports that there are several limitations to the use of mouse transgenic KO models. Mogil teaches that "the embryonic stem (ES) cell lines used to carry the targeted mutation are all derived from various substrains of the 129 strain" and "it is difficult to separate by homologous recombination the 129-derived transgene from tightly linked gene. Even after repeated backcrosses to C57Bl/6, a step most often omitted in the competition to publish, the wild-type and KO populations will differ in their inheritance of so-called "hitchhiking donor gene" alleles". Knockout mutant mice will inherit alleles tightly linked with the gene disruption, leading to "hitchhiking donor gene" alleles from 129 ES cell lines while the wild-type mice will inherit C57BL/6-derived alleles. "[O]bserved phenotypic differences between wild-type and KO mice could, therefore, be due to the targeted mutation, to allelic variation at one or more of the many unidentified hitchhiking genes, or to an interaction between them" (page 78, left column). In addition, "the background genes from the parent strains can interact with the targeted mutation ("epistasis"), importantly affecting the observed phenotype" (page 78, left column).

Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction). Leonard et al., 1995 (Immunological Reviews, Vol. 148, pages 97-114) disclosed mice with a disruption in the gc gene that was intended to be a model for X-linked severe combined immunodefkiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, lines 7-9). It appears that the resulting phenotype of a transgenic mouse was unpredictable at the time of the invention.

In view of the reasons set forth above, it is unclear whether a somatic or a germ line transgenic mouse could be made with the claimed method, whether the produced transgenic mouse would have a phenotype, and the resulting phenotype of the produced transgenic mouse was unpredictable at the time of the invention. Absent specific guidance for how to make a somatic transgenic mouse or a germ line transgenic mouse comprising the claimed 3' gene trap

cassette by using the claimed method and the lack of any phenotype of the transgenic mouse produced, one skilled in the art at the time of the invention would not know how to make and/or use the transgenic mouse produced by the claimed method, such as use for the study of basic biological processes and the development of therapeutics and diagnostics for diseases as disclosed in the specification. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

In addition, the claims encompass producing a transgenic mouse comprising the 3' gene trap cassette by using murine embryonic stem cells. Murine embryonic stem cells include mouse and rat embryonic stem cells.

Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) states that "animal transgenics is still suffering from technical limitations" (e.g. abstract). Gene replacement by homologous recombination in somatic mammalian cells has relatively poor efficiency and "For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells" (e.g. p. 148, right column). However, gene transfer or inactivation using embryonic cells has failed in species other than mouse, and "the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line...The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow now inclines to consider that the so- called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course" (e.g. p. 149, left column). Thus, the claimed method of using murine embryonic stem cells to make mutant mice via 3' gene trap cassette at the time of

the invention was not enabled other than the use of the two mouse lines mentioned by Houdebine.

The claims also encompass making somatic transgenic mouse, which is interpreted as chimeric mice (genetic mosaics) wherein only a portion of the cells of the mouse comprises the claimed 3' gene trap cassette. The specification fails to enable making chimeric mice by using the claimed method such that they exhibit any phenotype, including a wild-type phenotype. The specification fails to provide any guidance for how to make a somatic (chimeric) transgenic mouse by using the claimed 3' gene trap cassette via the claimed method. The specification does not correlate any phenotype to chimeric mice comprising one or more cells with the claimed 3' gene trap cassette. The method of making genetic mosaic mice is such that each resulting chimera is comprised of a different, unpredictable ratio of cells of various genotypes. This ratio cannot be predetermined. Furthermore, the spatial distribution of cells of each genotype cannot be predetermined. Therefore, the phenotype of chimeric animals is not only dependent upon the genotype of the cells (which is unpredictable as set forth by the state of the art outlined above, for example see Leonard; Mogil; Sigmund) but is also dependent upon the spatial distribution of the cells and their relative population size. Thus, the phenotype of the chimeric mice produced by the claimed method is highly unpredictable. The specification fails to provide the guidance necessary to overcome this high level of unpredictability to generate a chimeric mouse exhibiting any specific phenotype or any phenotype other than wild type. The specification discloses using the transgenic animals for the study of basic biological processes and the development of therapeutics and diagnostics for diseases. As set forth above, without a predictable phenotype, it would require additional and undue experimentation for one of skill in the art to determine a

useful phenotype for the chimeric mice produced by the claimed method and to determine what disease to study for.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the lack of guidance and working examples, the level of one of ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 34-39 and 42-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Zambrowicz et al., 2001 (US Patent No. 6,207,371 B1).

The applied reference has a common assignee and inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived

from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 34-39 and 42-46 are drawn to a method of making a transgenic mouse comprising a vector comprising a promoter, an exon sequence located 3' from said promoter and a splice donor sequence located at the 3' end of said exon sequence, by introducing said vector into murine embryonic stem cells, selecting a murine cell that comprises the vector and making a transgenic mouse from the selected murine ES cell. Claims 36, 37, 45 and 46 specify further identifying at least one trapped cellular exon. Claims 38 and 39 specify the transgenic mouse is a somatic transgenic mouse and a germ line transgenic mouse, respectively. Claims 42 and 43 specify the exon sequence encodes an enzymatic marker, a recombinase or a fluorescent marker. Claim 44 specifies the vector is a viral vector or a retroviral vector.

Zambrowicz discloses VICTR 3-5 gene trap vectors comprising a promoter, such as PGK promoter, a selectable marker, such as βgeo or HSV-Tk, and a splice donor sequence (e.g. column 7, lines 20-21, paragraph bridging columns 9-10, column 15, lines 41-54). The gene trap vector can be represented in retroviral form in retroviral vectors (e.g. column 7-8). Mouse ES cells are transfected with the gene trap vector to introduce mutation in the gene of the mouse genome and the ES cells can be injected into a blastocyst and become incorporated into normal development and ultimately the germ line so as to produce mutant transgenic mouse (e.g. column 15-16). Zambrowicz further teaches identifying mutated gene sequence in the genome by RT-PCR the mRNA isolated from the ES cells and using primers specific to the trapped, fusion transcript for PCR amplification and sequencing reaction to determine the sequence of the fusion

transcript (e.g. section 5.2.2, column 16-17). Thus, claims 34-39 and 42-46 are anticipated by Zambrowicz.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER